BIOTRUST RESEARCH MANUAL

Michigan BioTrust for Health

Michigan Department of Health and Human Services

Email: BioTrust@Michigan.gov
Phone: 866-673-9939
Website: Michigan.gov/BioTrust

Table of Contents

INTRODUCTION

The Michigan Newborn Screening (NBS) Program began in 1965 and screens all babies born in the State of Michigan for more than 50 rare but serious disorders that benefit from early diagnosis and treatment. Five to six drops of blood are collected from the heel of infants on filter paper and sent to the Michigan Department of Health and Human Services (MDHHS) laboratory for this testing. For more information on Michigan's NBS program, visit Michigan.gov/NewbornScreening.

Most dried blood spot (DBS) cards have whole or parts of spots that are left over after testing is complete. Following recommendations from the Governor's Commission on Genetic Privacy and Progress, the Michigan Legislature amended the Public Health Code in 2000 to allow for the use of these residual newborn screening blood spots in health research (MCL Section 333.5431). Subsequently, MDHHS developed the Michigan BioTrust for Health to oversee the use of these residual specimens in medical and public health research studies.

The primary goals of the BioTrust are to: (1) make blood spots more useful for medical and public health research while protecting privacy, (2) store blood spots to better preserve the samples, (3) encourage research, (4) engage and inform the public and (5) allow personal decision-making. Since 2010, residual blood spots from newborn screening in Michigan have been used in more than 70 medical and public health research studies. A list of all research studies that have utilized these specimens is maintained online in our BioTrust Research Report.

This manual is intended for use by investigators interested in learning more about the use of DBS from the Michigan archive for research studies. It provides detailed information on:

- Availability of DBS for research.
- Consent requirements for accessing DBS.
- Storage conditions of archived DBS.
- MDHHS policies related to DBS research.
- Research application processes.
- Charges related to DBS research.

THE MICHIGAN BLOOD SPOT ARCHIVE

The archive of residual DBS in Michigan contains specimens from more than 4 million persons born in Michigan since 1987. Each year, more than 100,000 DBS are collected for newborn screening and are added to the archive if any DBS remain after the necessary testing is complete.

Due to the growing size and technical expertise required to maintain and store the DBS archive, MDHHS established a relationship with a specialized storage facility—the Michigan Neonatal Biobank (MNB) around 2009. The MNB is a non-profit organization located at Wayne State University with the sole purpose of securely maintaining the archive of residual DBS from newborn screening. It provides secure, temperature and humidity-controlled environments for the archive. MNB receives DBS labeled with a code and is not granted access to any identifying information. MNB only releases blood spots to research studies under the direction and approval of MDHHS and the BioTrust program. For more information about the MNB, please visit MNB.Wayne.edu.

After establishing the storage facility at MNB, MDHHS began transferring over legacy DBS cards already in storage. As of July 19, 2022, 3.3 million DBS have been sent to MNB for long-term storage, and work is ongoing to process and transfer the remaining samples physically located at MDHHS. The BioTrust seeks to store DBS in conditions that best preserve the samples moving forward. The table below outlines current storage conditions of DBS cards based on the date of blood spot collection:

Date of DBS Collection:	Storage condition:
January 1987 through October 1995	Stored at MDHHS laboratory retention center in uncontrolled temperature/humidity environment or at MNB repository at ~70 degrees and ~35% humidity.
November 1995 through December 2008	Stored in MNB repository at ~70 degrees and ~35% humidity.
January 2009 through September 2010	Stored in MNB repository. Specimens were frozen (-20C) within 90 days of collection.
October 2010 to Current	Stored in MNB repository. Specimens were frozen (-20C) within 14 days of collection.

**Of note, any specimen collected between January 2009 and August 2012 and March 2020 through June 2020 may have undergone one to two freeze thaw cycles. Any specimen collected prior to January 2009 was originally stored in an uncontrolled temperature and humidity environment prior to shipment to MNB for long term storage. Further, only specimens collected after October 1987 may be available for research. Prior to October 1987, newborn screening was not centralized to the MDHHS laboratory and complete records may not be available.*

GUIDELINES FOR THE RESEARCH USE OF BLOOD SPOTS

MDHHS maintains multiple policies that outline appropriate DBS storage and uses during the retention period. These policies are approved by the MDHHS Institutional Review Board (IRB) and the BioTrust Community Values Advisory Board (CVAB).

According to MDHHS policy HPL 111, DBS can be stored for up to 100 years, with the current MDHHS retention schedule stating that blood spots will be destroyed after 35 years. MDHHS policy HPE 114 outlines the acceptable uses of dried blood spots from Michigan in research studies. Below is a brief overview of this research policy. It is strongly recommended that researchers planning to use blood spots in a project review this policy in detail.

Per the policy, research priorities for blood spots include but are not limited to:

- Prenatal, childhood or adult-onset disorders.
- Environmental exposures.

Research for the following purposes is expressly prohibited:

- Chemical, biological or nuclear warfare.
- Cosmetics.
- Other non-health related ventures unless for purposes related to injury or medical conditions.

Protecting confidentiality in all BioTrust research activities is critical. All research must be de-identified unless research teams obtain study-specific consent from each participant whose specimen they plan to access. This consent must include a written signature from the participant or a legal guardian authorized to act on their behalf.

The use of DBS in genomic analyses is similarly limited. Researchers seeking approval to utilize blood spots for whole genome or whole exome sequencing must obtain individual, study-specific, written consent prior to the release of specimens by MDHHS.

Prior to the release of any specimens for research purposes, investigators must first complete the BioTrust application process, which is described in detail starting on page 10. Research projects that do not satisfy the criteria in policy HPE 114 will **not** be considered by MDHHS.

BLOOD SPOT AVAILABILITY AND CONSENT REQUIREMENTS

De-identified Research Studies:

In de-identified research studies, the research team does not know whose blood spots are included in the study. Only MDHHS possesses the ability to link the DBS used and the identity of the person from whom the specimen originated.

The availability of specific blood spots for de-identified research depends upon the date that the sample was collected. The table below outlines the availability of blood spots based on date:

Date of DBS Collection:	**Availability of DBS for Research Purposes:**
Between October 1987 and April 2010	Blood spots collected in this period are generally available for de-identified research under a waiver of informed consent granted by the MDHHS IRB. However, individuals have the option to opt out of blood spot research by filing a form with MDHHS.
After May 2010	Blood spots are only available for use in de-identified research studies if a "Yes" BioTrust consent form is on file with MDHHS. This consent is collected by hospital staff and home birthing attendants within the time frame that screens are collected for NBS.

If planning a research study using DBS collected after May of 2010, it is important to consider that not all specimens are available, and this may affect random sampling techniques. Currently, a "Yes" BioTrust consent form is on file for more than 800,000 specimens. Moving forward, it is estimated that a "Yes" consent will be available for approximately 60 percent of newborn screening specimens collected each year.

Identified Research Studies:

Investigators who wish to access blood spots from specific individuals in an identified fashion must seek study-specific informed consent for such activities. Per BioTrust research policies, the consent must include a written signature from the participant or appropriate legal guardian. Consent forms must be reviewed and approved by the MDHHS IRB prior to use and must include sufficient language to describe the use of blood spots to the participant. Examples of language used in BioTrust-approved studies can be found in the appendix of this document. Prior to the release of any specimens, a copy of each signed consent form must be provided to MDHHS for review.

Data Availability:

Residual blood spots from NBS can be linked to MDHHS data sets to enable research teams to select specimens based on set criteria or to include data in project analyses. All data released is de-identified unless research teams specifically seek informed consent from each participant to allow access to identified data elements. For further protection of confidentiality, de-identified data provided with blood spots are subjected to BioTrust uniqueness testing protocols prior to release. In this process, the NBS epidemiologist working on the study ensures that the profile of data elements being released for sensitive variables, such as sex, race, and date-related elements, match at least four other persons in the eligible study population. Additionally, MDHHS will not release data to a research team until a data use agreement has been executed between MDHHS and the receiving institution. Inclusion of data sources beyond NBS may result in the need for additional approvals prior to execution of the study.

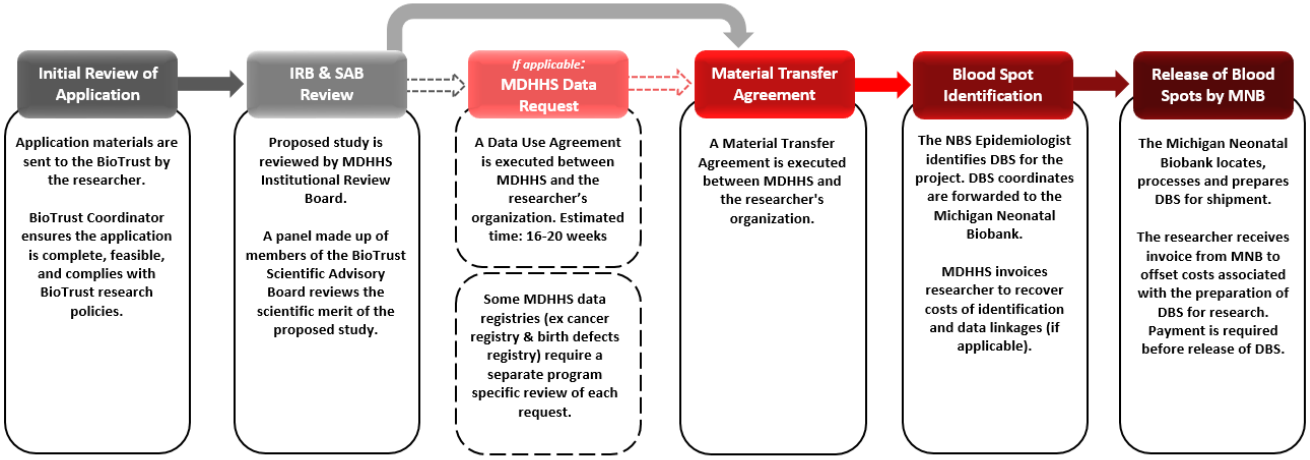
Blood spots have previously been linked to data from the following programs:

- Newborn screening: The Michigan NBS program maintains data related to the screening of all infants in the State of Michigan. The database includes demographic information, blood spot characteristics and collection information, and analyte data for the screened conditions.
- Vital Records (birth and death certificates): This data source serves as an important source of statistical information related to births and deaths occurring in the state of Michigan. DBS have been linked to these records to allow for access to an expanded group of demographic and outcome variables.
- Michigan Cancer Surveillance Program (MCSP): MCSP is a statewide, population-based cancer registry. Cancer cases are reported to MDHHS by health care providers throughout Michigan. DBS have been linked to MCSP records to identify specimens collected from persons who later went on to develop a cancer.
- Michigan Birth Defects Registry (MBDR): The MBDR tracks diagnoses of birth defects in Michigan children. The registry currently tracks more than 1,000 diagnoses and has been linked to DBS to allow researchers to study children with birth defects in the state.
- Medicaid claims: These records document health care claims made for patients in Michigan who are covered by Medicaid insurance.

For more information on what may be included in these data sets, to request codebooks (where available), or to inquire about data availability from other sources, email the BioTrust Coordinator at BioTrust@Michigan.gov. For many of the listed data sources, availability also depends on the date of specimen collection, as collected variables have changed over time.

RESEARCH APPLICATION PROCESS

DHHS's review of a research study is multifaceted, and project materials are facilitated through the process by the BioTrust Coordinator. Blood spots are not released for a specific research study until approval is granted by MDHHS. The image below provides an overview of the steps required to access blood spots from the Michigan BioTrust for Health. Additional details on each step will follow.



Steps of Review Process:

MDHHS Institutional Review Board (IRB)

The MDHHS IRB reviews each study requesting residual NBS blood spots for adherence to ethical guidelines and to ensure that subjects' rights are adequately protected. For additional information on the MDHHS IRB or to review monthly meeting dates, please visit www.Michigan.gov/IRB.

Timeline: The MDHHS IRB convenes on the first Tuesday of the month unless a schedule conflict is present. The schedule for MDHHS IRB meetings can be found online- IRB Monthly Meeting Dates (michigan.gov). Application materials must be submitted to the MDHHS IRB at least 10 business days prior to the next scheduled meeting. BioTrust staff require materials 15 business days prior to the next meeting to ensure adequate time to review materials for compliance with BioTrust policies. The MDHHS IRB does not participate in reliance agreements for any studies using DBS.

BioTrust Scientific Advisory Board (SAB)

The SAB evaluates each study protocol for scientific rigor, innovation and significance to health research, feasibility and consistency with MDHHS policies regarding the appropriate research use of

DBS. Reviewers employ a standard point scoring system ranging from one to seven, where one indicates the study has very few strengths and numerous major weaknesses and seven means the study is extremely strong with negligible weaknesses. Reviewers are asked to score the project on a range of topics including: whether the project has the ability to make original or significant contribution to the public's health or the understanding of the condition studied, whether the hypotheses and aims to be studied are clearly stated, and whether the proposed research is an appropriate use of residual DBS. Scores from all panel members are averaged to a final study score. Proposals that receive an average composite score of 4.5 or higher and a recommendation for approval from a minimum of two reviewers will be considered approved, contingent upon MDHHS IRB approval. Proposals receiving a score of 4.4 or lower will be considered disapproved, however a researcher has the opportunity to revise a protocol for further consideration

 Timeline: Generally, SAB panels are given four to six weeks to complete their review. All attempts are made to convene SAB panels concurrent to IRB review, but timelines are dependent on reviewer availability, complexity of the application and the number of applications in the queue at the time of submission.

Other MDHHS Program Advisory Boards

Additional MDHHS advisory boards and departmental approvals may be required for release of linked data, such as data from the Michigan Cancer Surveillance Program. These review panels are convened once MDHHS IRB approval is granted. The need for these reviews will be communicated to individual research teams once project details and application materials have been shared with BioTrust staff. These reviews are managed and overseen by areas outside of the BioTrust.

Agreements:

The following agreements may be executed once all MDHHS boards have approved of a research study:

1. Material Transfer Agreement (MTA): An MTA specific to the research study is executed between the MDHHS Bureau of Laboratories and the research and/or testing laboratory. Once approvals are in place and the MTA has been signed by the research or testing institution, the MDHHS Bureau of Laboratories will execute the MTA.

    Timeline: Final MTA execution at MDHHS takes approximately five to 10 business days.

2. Data Use Agreement (DUA): A DUA is only executed for studies that request data from MDHHS program areas along with the blood spots. Research studies requesting only blood spots and no accompanying data are not subject to DUA requirements. Where necessary, the DUA is

executed between MDHHS and the research organization. If a research study is requesting data elements, a DCH-1294 form will need to be included in the application materials. The BioTrust Coordinator can provide the necessary forms upon request. Project specific DUAs are submitted for review by the compliance office at MDHHS.

 Timeline: Final MTA execution at MDHHS takes approximately 5-10 business days.

Submitting a BioTrust Application:

Below is an outline of all documentation necessary for a BioTrust research application. Each application should include:

- MDHHS IRB Application: There are two forms available to request IRB review at MDHHS: (1) the MDHHS IRB Initial Review Application or (2) the MDHHS IRB Abbreviated Initial Review Application. If the research is being reviewed by another IRB, and the external IRB application specifically delineates how Michigan blood spots are going to be used, the Principal Investigator (PI) can submit the full external IRB application to MDHHS along with the MDHHS IRB Abbreviated Initial Review Application. If the research is not being reviewed by an external IRB or if the external IRB application does not clearly delineate how Michigan blood spots are going to be used, the MDHHS IRB Initial Review Application should be utilized. The MDHHS IRB webpage contains a useful references for selecting an application.
- BioTrust Request for Samples Form: This form requests specific details about the research study's proposed use of blood spots, including where DBS will be tested, the amount of the blood spot required for testing, any linked data being requested, and a brief description of the study to be included in the public BioTrust research report on the BioTrust webpage. The final page of this form includes a BioTrust Application Checklist.
- Principal Investigator Curriculum Vitae (CV): The SAB panel will consider the experience of the investigator to determine if completion of the project is feasible based on previous research activities and expertise.
- PI Certificate of Completion for Human Subjects Research Training: A copy of a human subjects training certificate is necessary for the IRB portion of the review process. More information about the required human research protection training is maintained on the MDHHS IRB webpage at Required Human Research Protections Training (michigan.gov). In short, MDHHS will accept certificates from CITI Program trainings, those offered through the U.S. Department of Health and Human Services Office for Human Research Protections (OHRP) or through a university established training program.

- Detailed Study Protocol: In addition to details on the entirety of the study, the protocol should clearly delineate how DBS from the BioTrust will be utilized in the research study. Details on availability of resources to conduct the research should also be included.
- If applicable, consent forms or other study documents: If the request will include identified blood spots and/or identified data, a copy of the consent form intended for use in the study must be included in the application packet submitted to the BioTrust. Additionally, any other study documents, such as surveys or data collection tools for the project, must also be included. The BioTrust review process is intended to review the entirety of the study, not just portions related to blood spot analyses.

To access the necessary forms, download them from the Michigan BioTrust for Health- Dried Blood Spot Research page or email the BioTrust Coordinator. BioTrust research applications can be submitted directly to the BioTrust Research Coordinator at biotrust@michigan.gov. Once documentation for a study has been submitted, the BioTrust Coordinator will do an initial review of all documents. Following the initial review, the coordinator will respond with any questions on the application and an estimated timeline for review by both the MDHHS IRB and the BioTrust SAB.

BioTrust Application Checklist:

- ☐ MDHHS IRB application (Full or Abbreviated)
- ☐ BioTrust request for samples form
- ☐ Principal investigator CV
- ☐ Principal investigator required human subjects research protection training certificate
- ☐ Detailed and comprehensive study protocol

Steps Following Application Approval:

Once a research study has received full MDHHS approvals and all necessary agreements have been executed, BioTrust staff will work with the research team to identify the blood spots and any associated data needed for the study. The NBS Epidemiologist will perform blood spot identification steps for each study based on the criteria set forth the in the approved application. If necessary, this includes coordination with other involved MDHHS data sets.

If identified blood spots are being accessed, the research team will work with the BioTrust coordinator to securely share the following information:

- A copy of the signed consent for each DBS requested.

- A spreadsheet with as many of the following elements as possible:
    - Research ID.
    - Child's full name.
    - Child's date of birth.
    - Child's sex assigned at birth.
    - Mother's full name.
    - Hospital/location of birth.

Once blood spots have been selected for the project (whether identified or de-identified), the NBS epidemiologist will prepare the final study file. After the final file of blood spot codes is prepared, the BioTrust Coordinator will send the file and notice of approvals to the Biobank. Within this file, MDHHS shares the codes for the necessary blood spots with the MNB. MNB utilizes these codes to release the appropriate specimens to individual research studies once instructed by MDHHS.

The MNB staff will prepare specimens for the research project and communicate directly with the research team prior to sending blood spots to the testing laboratory. Once all necessary details are confirmed, DBS will be shipped to the testing lab labeled only with a code. For de-identified research studies, this research code will be assigned at random by the Biobank and will not be related to any identifying information. For research projects requesting a group of identified specimens, MNB will label each blood spots with the ID assigned by the research team and provided to MDHHS with other identifiers for specimen locating.

FEES ASSOCIATED WITH BIOTRUST RESEARCH

There are costs associated with performing research using DBS from the Michigan BioTrust for Health archive. Two separate cost recovery fees will be assessed to the research team following approval of an application.

MDHHS Cost Recovery Charge:

MDHHS has implemented the following cost recovery structure to recuperate costs associated with staff time invested in securing approvals, executing agreements and selecting specimens for use in research studies utilizing DBS through the Michigan BioTrust for Health. MDHHS does not profit from research using residual DBS. MDHHS program areas covered by the cost recovery schedule include: (1) Division of Lifecourse Epidemiology and Genomics and (2) Newborn Screening Section of the Division of Clinical Chemistry and Toxicology.

Under this schedule, the following structure is used to estimate the cost recovery charge for each individual research request. The hourly rate is $75/hour.

1. An application coordination charge of three hours at the hourly rate will be applied to each study. This charge is intended to recover the cost of staff time invested in ensuring that all regulatory approvals are in place prior to the release of blood spots for a study.
2. The structure below is used to estimate additional costs associated with staff time for individual requests:
    - Random samples – cohort
        - Three hours
    - Random samples – case-control
        - Six hours (includes matching on up to three variables)
        - One hour for each additional three matching variables
    - Consented population
        - Six hours (for up to 100 subjects)
        - One hour for every additional 100 subjects
    - Linkage to any dataset
        - Three hours per dataset
    - Any additional variables
        - One hour for every five variables
    - Additional complexity charge

- Additional hours will be charged for studies with unique/complex requests. Examples include time spent looking for diagnosed/positive cases, time spent verifying data received from researchers and time spent by NBS lab staff to process samples still in storage at MDHHS.

A quote for the MDHHS cost recovery charge will be provided for an individual research study upon request or at the time the full application is received for review by MDHHS. To request a quote, please contact the BioTrust coordinator with study details at biotrust@michigan.gov.

Please note there may be additional cost recovery charges assessed separately for linkage of DBS to other MDHHS data systems or registries not covered in the above structure. Upon inquiry, quotes will be provided for each additional program area involved.

Michigan Neonatal Biobank Fees:

The MNB charges an administrative fee to researchers performing MDHHS approved research studies using DBS. This fee helps offset the cost of storage, labor and shipping and is charged separately from the cost recovery charge issued by MDHHS. For additional information or a quote, please contact the Michigan Neonatal Biobank at mnbb@wayne.edu.

APPENDIX

Study Specific Consent Examples:

Below are three examples of language used in previous study specific consent forms that describe the use of residual DBS to study participants. These are intended to be used as a starting point for developing language specific to your own project. All consent language will be reviewed by the MDHHS IRB prior to being implemented in the field.

Example 1:

Neonatal blood spots – you will provide study staff permission to access a sample of the already collected neonatal blood spots from the State of Michigan. For all births in Michigan, blood is collected from a baby's heel shortly after birth to diagnose disorders that need early treatment. After coding to protect your privacy, blood spots leftover after newborn screening can be used for research through the Michigan BioTrust for Health program. We are requesting your permission to allow researchers the ability to access your child's identified blood spots. We need the spots to be identified so that we can connect information to other information that you may provide us during this research study. We will use the smallest amount we can from the blood spots, but we may have to use all of your child's leftover blood spots that have been reserved for research. Our purpose for the use of blood spots is to analyze proteins and epigenetic changes at the time of birth and their association with 1) placental markers and characteristics, 2) the prenatal environment, and 3) later risk of neurodevelopmental delays such as autism spectrum disorder.

Example 2:

By examining the information that has been provided to us, we can find out whether diet, genes, environmental chemicals, infections, hormones and more might lead to illnesses in children such as asthma, obesity or problems in physical, intellectual, or social development. Six drops of blood are collected from a baby's heel shortly after birth to diagnose disorders that need early treatment. After coding to protect your privacy, blood spots leftover after newborn screening can be used for research through the Michigan BioTrust for Health program. When your child was born, their mother may have been asked if you would allow your child's leftover spots to be available for research through the BioTrust. That consent is for use of blood spots that are not identified, where the researcher does not know whose blood spot is being used. We now ask permission to gain access to your child's identified leftover blood spots. We need the spots to be identified so that we can connect information from the spots to other information you provide us with during ARCH. We will use the smallest amount we can

from the blood spots, but we may have to use all of your child's leftover blood spots that have been reserved for research.

Blood spots will only be used for research on mother and child health such as we described above. There are many different types of laboratory methods that we might use in the future that can study factors such as genes, environmental chemicals, and more. Once these spots are provided to CHARM, they will be coded with a unique identification number so that researchers doing specific projects will not see you or your child's name. For extra protection, *each* blood spot project must be approved by MDHHS to make sure your privacy is protected, and that the scientific work has merit. In order to access these blood spots we will ask you to provide the hospital at which your child was born and the child's biological mother's full name at the time of your child's birth.

Example 3:

Bloodspots: You will be asked to allow us to use one of the newborn dried bloodspots that is collected when your child is born as well as a bloodspot from your own birth (if you were born in Michigan after October 1987). The Michigan Newborn Screening Program collects bloodspots soon after a baby is born in the hospital, from your baby's heel. This is required by state law and screens all babies for rare diseases to ensure early treatment. If there is blood leftover after newborn screening, it is stored by the Michigan BioTrust for Health. We are requesting your permission to have access to you and your baby's bloodspots to use for this research. We are not performing the blood draw or asking you for additional blood samples, only to have access to what is already there. We can only access bloodspots stored by the Michigan BioTrust for Health with your permission. We are using these spots to measure telomere length when you and your child were born. In addition, we may use these spots to measure epigenetic changes, such as DNA methylation, and persistent organic pollutants.